# No Residual Disease: The New Definition for Optimal Cytoreduction in Ovarian Cancer?

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## Introduction

Ovarian cancer is the deadliest gynecologic malignancy in the United States, with an estimated 22,240 new cases and 14,030 deaths in 2013.[1] In the 1970s, women with ovarian cancer had an average 5-year overall survival of 36%.[1] Modest improvement has been made in the past 40 years, with the average 5-year survival now reaching 43%.[1] Several advances have led to better outcomes. These include more uniform efforts to render ovarian cancer patients optimally debulked, the introduction of platinum and taxane agents into frontline treatment, the adoption of dose-dense and intraperitoneal chemotherapy strategies, and the development of other active agents for the treatment of ovarian cancer.

## Discussion

### *Evolution of the Definition of "Optimally Debulked" to ≤ 1 cm Residual Disease*

Abundant evidence suggests that optimal cytoreduction is the key to achieving the best outcome in ovarian cancer. The controversy lies in the definition of "optimal cytoreduction" and the strategy by which it can be accomplished. As early as 1975, it was recognized that survival was inversely related to residual tumor size; patients with residual tumor deposits > 1.5 cm had a poorer prognosis compared with those with < 1.5 cm in residual disease.[2] With improvements in surgical technique, critical care, and postoperative support, more aggressive surgery was possible, and the definition of "optimal cytoreduction" evolved.

In 1994, Hoskins and colleagues performed an ancillary study of Gynecologic Oncology Group (GOG) study 97 and found that women who had residual tumor deposits < 1 cm had improved survival compared with women with a larger disease burden, setting the current defined standard for "optimally debulked" ("optimal") as < 1 cm residual disease.[3] Chi and colleagues confirmed this in 2001, publishing their experience of 282 patients with advanced-stage ovarian cancer.[4] Among 18 factors evaluated in their multivariate analysis, only age, ascites, and residual disease were determined to correlate with prognosis. Ovarian cancer patients with stage III disease who underwent an optimal debulking had a median survival of 56 months compared with 31 months in women with gross residual disease. There was no difference in median survival in women with 1 to 2 cm of residual disease compared with those with > 2 cm of residual disease. Of note, only 25% of their study population had an optimal cytoreduction, which the authors partially attributed to the nonuniform definition of "optimal." More than a decade later, this confusion continues to pose an issue.

### *Evidence for Defining "Optimally Debulked" as No Residual Disease*

Aggressive cytoreduction to achieve no gross residual disease (NRD) was a natural extrapolation from data that suggested an inverse linear relationship between survival and residual disease. Eisenkop et al. reported their experience with attempted complete cytoreduction in 163 patients.[5] They achieved NRD in 85.3% (139 of 163) of their patients, although this was tempered by fairly high surgical morbidity. Survival significantly correlated with cytoreduction, with a hazard ratio of 2.14 in patients who were not disease-free at the completion of primary surgery. Bristow and colleagues performed a meta-analysis of the available cytoreduction evidence in 2002.[6] Their results showed that for every 10% increase in maximal cytoreduction, the median survival increased by 5.5%. Patient cohorts with a ≤ 25% maximal cytoreduction had a median survival of 22.7 months, whereas cohorts with a > 75% maximal cytoreduction had a 50% longer median survival of 33.9 months.

Further evidence that patients who are visibly disease-free at the completion of primary surgery have a significantly better overall survival than patients who have any macroscopic disease comes from GOG trials 104 and 172.[7,8] Both trials demonstrated the overall survival superiority of intraperitoneal (IP) chemotherapy in primarily optimally debulked patients. Subanalysis of those patients who underwent cytoreduction to only microscopic disease showed an even more pronounced survival benefit. Impressively, patients in GOG 172 who had no residual disease and received IP therapy had not reached a median survival at the time of publication in 2006,

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5 years after the trial closed to accrual.[8] Combining a superior chemotherapy regimen with maximal cytoreduction likely has the greatest impact on overall survival.

### *Role of Neoadjuvant Chemotherapy in Achieving Optimal Debulking*

There are ovarian cancer patients who cannot tolerate aggressive primary surgery or who are not able to be optimally debulked, no matter how aggressive the surgeon may be. Ovarian cancer patients with significant comorbidities may fare worse with extensive surgery. Those who have significant pulmonary or intrahepatic disease burdens pose a surgical challenge. Bristow et al. and Winter et al. separately published series on patients with stage IV ovarian cancer and found that women with extensive suboptimally debulked hepatic metastases did worse than women who had complete resection of all disease.[9,10] Winter et al. went as far to suggest that ultraradical surgery should only be considered in selective ovarian cancer patients "in whom microscopic residual disease is possible."[10]

Neoadjuvant chemotherapy has been suggested as an alternative to surgery for those patients who have significant medical comorbidities or in whom a reasonable attempt at primary complete cytoreduction is not feasible. Two large multinational trials have examined the efficacy of neoadjuvant chemotherapy followed by interval debulking surgery (IDS) in patients with advanced-stage ovarian cancer. The European Organization for Research and Treatment of Cancer (EORTC) trial compared the effect of 6 cycles of neoadjuvant cyclophosphamide and cisplatin to 3 cycles of neoadjuvant chemotherapy followed by IDS and an additional 3 cycles.[11] Women who had small-volume disease prior to IDS had a similar overall survival to women who had an optimal IDS. Both of these groups had a superior overall survival compared with women who had a suboptimal IDS or who did not have surgery at all. Vergote and colleagues published a randomized trial comparing primary debulking surgery and platinum-based neoadjuvant therapy followed by IDS and found that survival was equivalent in both groups.[12] A common criticism of both of these trials is that patients were not necessarily treated by gynecologic oncologists; it is possible that women did not undergo primary maximal surgical effort, which could account for the nonsuperiority of initial cytoreduction. In a 2009 meta-analysis of neoadjuvant studies, Kang and colleagues reported that while it did not improve overall survival, neoadjuvant chemotherapy decreased the odds of a suboptimal cytoreduction.[13] Taken together, this data suggests that maximal surgical effort should be primarily exerted if the patient can be rendered disease-free. In the face of apparently unresectable disease, however, patients may benefit from neoadjuvant chemotherapy followed by an aggressive cytoreduction with no residual disease being the goal.

### *Defining a New Paradigm for Achieving NRD-Defined Optimal Debulking*

The optimal paradigm of treating women with newly diagnosed advanced-stage ovarian cancer remains elusive. However, certain tenets are becoming clear. It is apparent that women whose disease burden can be reduced to microscopic disease have a significant survival advantage. How that is best achieved is still controversial. Women who present with small-volume disease fare best, as their surgeries are less complicated and complete resection is more frequently achieved. In women with large-volume disease, complete resection is less feasible. Could NRD be obtained in women with initially unresectable disease with neoadjuvant chemotherapy followed by an interval attempt at cytoreduction? Available evidence suggests that this may indeed be the case.

If NRD is the ultimate goal, then does it matter how it is achieved? In patients who are too sick to undergo aggressive surgery and the morbidity it entails or who appear to have disease not amenable to being optimally cytoreduced, neoadjuvant treatment (whether conventional or a dose-dense paclitaxel regimen) should be given to reduce tumor burden while the patient's performance status improves. At the time of IDS, if NRD is achieved, why not denote this time as "point zero" and treat the patient as someone who achieved NRD at primary surgery? This could conceivably entail placement of an IP catheter with plans to treat with up to 6 cycles of intraperitoneal chemotherapy, an approach demonstrated to be effective in a recent phase II trial.[14] Alternatively, a dose-dense paclitaxel regimen the patient may have received prior to surgery could be continued. Achieving NRD, regardless of how a patient gets there, is of paramount importance in the treatment of this disease. Such an approach may result in potentially more therapy. That said, the argument could be made that a patient who was suboptimally debulked was going to receive more than 6 cycles of standard chemotherapy treatment to control her disease regardless, and the survival benefits of an NRD strategy have been clearly demonstrated.

## Conclusion

The landscape of health care is rapidly changing. Resources are increasingly limited and rational quality indicators need to be defined for the management of patients with ovarian cancer. If NRD is the ideal therapeutic goal, it may be that neoadjuvant chemotherapy followed by IDS in patients with large-volume disease is a way to improve quality while containing costs. The ideal neoadjuvant and adjuvant regimens in ovarian cancer are still being defined, and emerging data regarding dose-dense paclitaxel therapy and biologics such as bevacizumab need to be incorporated into these paradigms. Research defining which treatments are cost-effective while maximizing patient outcomes is desperately needed.

Ovarian cancer patients deserve the best chance at optimizing their survival. The first step to providing this is achieving optimal cytoreduction and preferably eradicating all visible disease. Whether it is best achieved through a primarily surgical approach or a combined neoadjuvant chemotherapy/IDS depends on the patient. As the biology of ovarian cancer is better elucidated, we will be better able to choose which patients will benefit most from each option.

## Disclosure

The authors have stated that they have no conflicts of interest.

## References

1. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. *CA Cancer J Clin* 2013; 63:11-30.
2. Griffiths CT. Surgical resection of tumor bulk in the primary treatment of ovarian carcinoma. *Natl Cancer Inst Monogr* 1975; 42:101-4.
3. Hoskins WJ, McGuire WP, Brady MF, et al. The effect of diameter of largest residual disease on survival after primary cytoreductive surgery in patients with suboptimal residual epithelial ovarian carcinoma. *Am J Obstet Gynecol* 1994; 170: 974-9; discussion 979-80.

4. Chi DS, Liao JB, Leon LF, et al. Identification of prognostic factors in advanced epithelial ovarian carcinoma. *Gynecol Oncol* 2001; 82:532-7.
5. Eisenkop SM, Friedman RL, Wang HJ. Complete cytoreductive surgery is feasible and maximizes survival in patients with advanced epithelial ovarian cancer: a prospective study. *Gynecol Oncol* 1998; 69:103-8.
6. Bristow RE, Tomacruz RS, Armstrong DK, Trimble EL, Montz FJ. Survival effect of maximal cytoreductive surgery for advanced ovarian carcinoma during the platinum era: a meta-analysis. *J Clin Oncol* 2002; 20:1248-59.
7. Alberts DS, Liu PY, Hannigan EV, et al. Intraperitoneal cisplatin plus intravenous cyclophosphamide versus intravenous cisplatin plus intravenous cyclophosphamide for stage III ovarian cancer. *N Engl J Med* 1996; 335:1950-5.
8. Armstrong DK, Bundy B, Wenzel L, et al. Intraperitoneal cisplatin and paclitaxel in ovarian cancer. *N Engl J Med* 2006; 354:34-43.
9. Bristow RE, Montz FJ, Lagasse LD, Leuchter RS, Karlan BY. Survival impact of surgical cytoreduction in stage IV epithelial ovarian cancer. *Gynecol Oncol* 1999; 72:278-87.
10. Winter WE 3rd, Maxwell GL, Tian C, et al. Tumor residual after surgical cytoreduction in prediction of clinical outcome in stage IV epithelial ovarian cancer: a Gynecologic Oncology Group study. *J Clin Oncol* 2008; 26:83-9.
11. van der Burg ME, van Lent M, Buyse M, et al. The effect of debulking surgery after induction chemotherapy on the prognosis in advanced epithelial ovarian cancer. Gynecological Cancer Cooperative Group of the European Organization for Research and Treatment of Cancer. *N Engl J Med* 1995; 332:629-34.
12. Vergote I, Trope CG, Amant F, et al. Neoadjuvant chemotherapy or primary surgery in stage IIIC or IV ovarian cancer. *N Engl J Med* 2010; 363:943-53.
13. Kang S, Nam BH. Does neoadjuvant chemotherapy increase optimal cytoreduction rate in advanced ovarian cancer? Meta-analysis of 21 studies. *Ann Surg Oncol* 2009; 16:2315-20.
14. Tsubamoto H, Itani Y, Ito K, Kanazawa R, Toyoda S, Takeuchi S. Phase II study of interval debulking surgery followed by intraperitoneal chemotherapy for advanced ovarian cancer: a Kansai Clinical Oncology Group study (KCOG9812). *Gynecol Oncol* 2013; 128:22-7.